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# Clinical research in pediatric organ transplantation

Estela Azeka,<sup>1</sup> Laura Castillo Saavedra,<sup>11</sup> Felipe Fregni,<sup>11\*</sup>

<sup>1</sup>Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Heart Institute (InCor), São Paulo/SP, Brazil. <sup>11</sup>Harvard Medical School, Spaulding Rehabilitation, Hospital Laboratory of Neuromodulation, Boston, USA.

Solid organ transplantation has greatly improved survival in children with end-stage disease, becoming one of the main treatment options in this population. Nonetheless, there are significant challenges associated with validating and optimizing the effects of these interventions in clinical trials. Therefore, we reviewed the main issues related to conducting clinical transplantation research in children. We divided these challenges into three different categories: (i) challenges related to surgical techniques and anesthetic procedures, (ii) challenges related to post-transplant care and (iii) challenges specific to a particular population group and disease type. Some of the observed burdens for clinical research in this field are related to the limitations of conducting studies with a placebo or sham procedure, determining the standard of care for a control group, low prevalence of cases, ethical concerns related to use of a placebo control group and lack of generalizability from animal studies and clinical trials conducted in adult populations. To overcome some of these barriers, it is necessary to utilize alternative clinical trial designs, such as observational studies or non-inferiority trials, and to develop multicenter collaborations to increase the recruitment rate. In conclusion, the lack of robust data related to pediatric transplantation remains problematic, and further clinical trials are needed to develop more efficacious and safer treatments.

**KEYWORDS:** Organ Transplantation; Clinical Research; Children; Clinical Trial; Immunosuppression.

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E-mail: felipe.fregni@ppcr.hms.harvard.edu/fregni.felipe@mgh.harvard.edu

\*corresponding author

Tel.: (617) 952-6156/(617) 952-6153

## ■ INTRODUCTION

Solid organ transplantation has become the mainstay of treatment for children with end-stage heart, kidney, lung and liver diseases, improving survival and life expectancy in up to 80% of patients. The history of solid organ transplantation dates back to 1952, when the first pediatric kidney transplant was performed (1), followed by the first liver transplant in 1963 (2) and the first heart transplant in 1967 (3). Since these early successes, the development and constant improvement of surgical techniques, anesthetic procedures (4-6) and post-transplantation care, especially immunosuppressive therapy, have greatly increased the rate of graft success and have improved recipient outcomes (7-10).

Despite the progress made in the field of pediatric transplantation in recent years, the clinical development of this therapeutic approach remains a fundamental challenge, mainly due to inherent issues related to conducting clinical transplantation research in children. These issues can be categorized as those associated with the study of surgical

techniques and anesthetic procedures, those related to post-transplant care, including the study of immunosuppressive therapy, and challenges specific to the disease type and population group.

## ■ CHALLENGES FOR SURGICAL AND ANESTHETIC TECHNIQUE RESEARCH

Research exploring surgical techniques for pediatric solid organ transplantation poses several burdens on researchers. For example, the use of placebo or sham procedures is both ethically and logistically unviable, making it impossible to include a control group in clinical trials. It is also difficult to establish a clear definition for standard of care due to the constant evolution of surgical techniques, innovation in operative instruments, changes in the criteria for donor and recipient selection, improvements in perioperative management and the continuing perfection of anesthetic procedures. Consequently, the comparability and translation of the results is limited. Due to the low number of cases per year, most clinical trials resort to the use of multiple research centers to meet their participant accrual and enrollment requirements, which can introduce bias to the study related to the variability in surgical procedures among centers and the grade of expertise among surgeons.

Conducting observational studies is valuable; however, similar confounders, mainly those associated with variability in donor and recipient selection criteria and in surgical

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technique and expertise among centers, can obscure and limit the results.

## ■ CHALLENGES FOR POST-TRANSPLANT CARE RESEARCH

Post-surgical management is an essential part of transplant care, and a high percentage of the success of solid organ transplants can be attributed to the improvement in peri- and post-operative care of these patients, including immunosuppression therapy. Research studies evaluating the efficacy and safety of immunosuppressive therapies for solid organ post-transplant care are difficult to design and conduct (11). Most of the challenges associated with this type of trial are related to ethical concerns of using placebo in the control group. Only a few randomized clinical trials have been conducted, and most of these compare a new intervention combined with standard treatment to standard treatment alone (12,13) or opt for a non-inferiority design, comparing the new intervention to standard treatment (14). The main limitations of these two types of designs are the large sample size required to achieve good power and poor generalizability of the results because of the strict selection criteria and lack of a true placebo-control group. Due to these limitations, most researchers opt for observational studies; however, this type of design has inherent restrictions associated with the effects of potential confounders on the results.

The lack of consensus and standardization of post-transplant care in pediatric patients is also a major limitation for the design of clinical trials and for drawing conclusions that can be used in the clinical setting. A recent systematic review conducted by Gijzen et al. (15) reported a wide range of definitions for inclusion criteria and high variability among measurements in the 18 trials included, demonstrating that these disparities can be a significant barrier to the improvement of clinical research in pediatric transplantation. Similar findings were reported by Rothbaum and colleagues (16), emphasizing the lack of strong evidence in the field.

Results from *in vitro* studies and animal models cannot always be translated to *in vivo* outcomes, mainly because they are unable to accurately predict the effects of new therapeutic molecules in the dynamic donor-recipient relationship or reflect their influence on disease type and severity. Extrapolation of the results from research exploring similar diseases is not always possible because of the specific effects of this therapeutic procedure on the pathophysiological mechanisms of each condition.

## ■ CHALLENGES INHERENT TO DISEASE TYPE AND POPULATION GROUP

Most clinical trials and observational studies in this field include only adult participants; these studies are commonly used as guidelines for decision-making related to transplantation in children. However, the generalizability of results obtained with adults to pediatric populations is limited and should be assessed carefully. The effects and success of transplantation in children can significantly differ from that in adults, mainly because of specific aspects such as growth and development, differences in the classification of severity in end-stage diseases and criteria for recipient

selection, which can highly influence graft viability and success.

The small number of solid organ transplantations performed in pediatric patients per year remains an important challenge for research in this field, and it is even more evident when the analysis is focused on organs such as the heart and lung. Sweet et al. (17) reported that 125 pediatric lung transplantations were performed annually worldwide, with an average of 2-3 transplants per center per year.

Randomization of children in the context of a clinical trial poses major ethical concerns, especially when new interventions are being tested. Obtaining informed consent either from the subjects themselves or from parents and legal guardians is a major barrier for randomized clinical trials (RCTs) in pediatric populations (18,19). The Zelen design was implemented as an alternative to conventional RCTs, allowing researchers to seek consent from the patient or parents after randomization is completed. Therefore, participants are asked to consent to receiving a specific treatment and not to being randomized in the trial, which increases the accrual rate given that subjects are aware of their allocation at the moment of consent. The first example of this randomization approach was the extracorporeal membrane oxygenation trial, which tested the effects of extracorporeal membrane oxygenation in neonates with severe pulmonary hypertension (20). To date, no adaptations of the Zelen design have been reported in the transplant literature.

## ■ STRATEGIES FOR OVERCOMING CHALLENGES IN PEDIATRIC ORGAN TRANSPLANT RESEARCH

Given all of these challenges, researchers in pediatric transplantation should be aware of potential alternatives that can aid in overcoming the barriers to clinical research in this field. Such alternatives should be implemented whenever possible.

Observational studies can be a solution for overcoming ethical concerns related to RCTs. These studies should be carefully designed, and researchers must be aware of and actively think about potential confounders that may obscure the results. These potential cofounders should be accounted for both at the moment of design and during data analysis. The development of pragmatic trials can also be an alternative to research in pediatric transplantation, as they allow the effects of an intervention to be studied in real-life routine practice conditions and can be extended to more complex and robust explanatory trials.

As previously mentioned, some of the limitations of RCTs, both in surgical and clinical scenarios of pediatric transplantation, are associated with the inability to translate the results obtained from adult studies and from pediatric studies examining similar diseases and procedures. For researchers to overcome these barriers, it is necessary to have a clearer understanding of the mechanisms that determine success or failure of transplantation in children and how they differ from those in adults and in other diseases.

Another major challenge is related to the small number of pediatric transplantation cases per year. Several initiatives have been created to aid this purpose, with the aim of consolidating a strong network of transplant centers with unified criteria for patient selection, standard surgical procedures and post-operative care. These initiatives also



aim to create a large registry of pediatric solid-organ transplant recipients for future observational research in the field. For example, the International Pediatric Lung Collaborative (IPLTC) (17) and the Pediatric Heart Transplant Study Group (PHTS) (21) were created for this purpose and have been successful in terms of consolidating a strong database for observational studies in this area. The National Institute of Allergies and Infectious Diseases designed a helpful strategy that aims to increase the number of trials conducted in pediatric transplant recipients, referred to as Clinical Trials in Organ Transplantation in Children (CTOT-C) (22). The goal of this initiative is to improve the understanding of the immune factors that play a role in transplant success. To date, approximately 10 clinical trials have been approved and are actively recruiting. More than 70 research centers in 50 different academic institutions are involved in this initiative.

In conclusion, there are fundamental challenges related to the design and execution of clinical trials and observational studies for pediatric solid-organ transplantation. Efforts should be made to develop alternatives that can help researchers overcome some of these challenges so that evidence in this field can be strengthened and clinical practice can be based on robust results from well-designed studies.

## AUTHOR CONTRIBUTIONS

Azeka E conceived the study, performed the literature review and wrote the manuscript. Saavedra LC performed the literature review and wrote the manuscript. Fregni F conceived the study, wrote the manuscript, revised it critically for important intellectual content and approved the final version.

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